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Health and Environmental Effects Profile for 2-Methoxyethanol Acetate

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16. ABSTRACT

The Health and Environmental Effects Profile for 2-Methoxyethanol Acetate was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA) and to provide health-related limits for emergency actions under Section 101 of the Comprehensive Environmental Response, Compensation and Liability Act (CERCLA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents. Quantitative estimates have been presented provided sufficient data are available. 2-Methoxyethanol acetate has been determined to be a systemic toxicant. A Reference Dose (RfD), defined as an estimate (with uncertainty spanning perhaps an order of magnitude) of the daily exposure to the human population (including sensitive subgroups) that is likely to be without appreciable risk of deleterious effect during a lifetime, for 2-methoxyethanol acetate is 0.002 mg/kg/day for inhalation exposure. The Reportable Quantity (RQ) value of 1, 10, 100, 1000 or 5000 pounds is used to determine the quantity of a hazardous substance for which notification is required in the event of a release as specified by CERCLA based on chronic toxicity. The RQ value for 2-methoxyethanol acetate is 100.

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ENVIRONMENTAL CRITERIA AND ASSESSMENT OFFICE
OFFICE OF HEALTH AND ENVIRONMENTAL ASSESSMENT
OFFICE OF RESEARCH AND DEVELOPMENT
U.S. ENVIRONMENTAL PROTECTION AGENCY
CINCINNATI, OH 45268

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Scientists from the following U.S. EPA offices provided review comments for this document series:

Environmental Criteria and Assessment Office, Cincinnati, OH
Carcinogen Assessment Group
Exposure Assessment Group
Reproductive Effects Assessment Group

Editorial review for the document series was provided by:
Judith Olsen and Erma Durden
Environmental Criteria and Assessment Office, Cincinnati, OH

Technical support services for this document series were provided by:
Bette Zwayer, Pat Daunt, Karen Mann, and Jacky Bohanon
Environmental Criteria and Assessment Office, Cincinnati, OH.

EXECUTIVE SUMMARY

2-Methoxyethanol acetate, also known as ethylene glycol monomethyl ether acetate, is a colorless liquid at room temperature, with a sweet, pleasant odor. It is miscible with water and many common organic solvents (Verschueren, 1983; Hawley, 1981). Ethylene glycol monomethyl ether, formed by reacting ethylene oxide and anhydrous methanol, is esterified with acetic acid to produce 2-methoxyethanol acetate (U.S. EPA, 1982). As of 1984, Union Carbide Corp., South Charleston, WV, was the sole U.S. manufacturer of 2-methoxyethanol acetate. The current U.S. production volume for this chemical is unavailable.

The primary use of 2-methoxyethanol acetate is as a solvent for oils, greases, inks, gums, resins, plastics, adhesives, waxes, nitrocellulose, cellulose acetate and other cellulose esters and ethers. 2-Methoxyethanol acetate is also used in the manufacture of lacquers, enamels, adhesives, photographic film and in the textile printing industry (U.S. EPA, 1982).

If released to water, the primary processes that may remove 2-methoxyethanol are hydrolysis and biodegradation (Lyman et al., 1982). Bioaccumulation in aquatic organisms and adsorption to suspended solids and sediments should not be significant. The compound is expected to persist in aquatic media. If released to the atmosphere, 2-methoxyethanol acetate is expected to exist primarily in the vapor phase and is apparently susceptible to oxidation by HO radical ($t_{1/2}$=22.42 hours) (Yanagihara et al., 1977; U.S. EPA, 1986b). Removal from the atmosphere by wet deposition may also be significant. If released to soil, 2-methoxyethanol acetate should be highly mobile in moist soils and may volatilize significantly from dry soil surfaces. This compound may be degraded in moist soils by hydrolysis and biodegradation.

Limited monitoring and exposure data regarding 2-methoxyethanol acetate were located in the available literature. 2-Methoxyethanol acetate has been qualitatively identified in drinking water (Kool et al., 1982) and in an effluent discharged into the Illinois River (Somani et al., 1980). It is likely that consumer exposure to this compound will occur during the use of cleaning solutions, paint, ink and nail polish (U.S. EPA, 1982).

Potential routes of 2-methoxyethanol acetate exposure to workers include inhalation of the vapor, ingestion and eye and skin contact (U.S. EPA, 1982). A 1972-1974 National Occupational Hazard Survey estimated that 436,989 workers are occupationally exposed to this compound during manufacturing, processing, use and handling of 2-methoxyethanol acetate (RTECS, 1984). A more recent survey, the National Occupational Exposure Survey, estimates that 2024 workers are exposed to 2-methoxyethanol acetate; however, this figure does not reflect exposure to tradename products containing 2-methoxyethanol acetate (NIOSH, 1985).

Little information is available concerning effects of 2-methoxyethanol acetate on aquatic organisms. LC_{50} values of 40, 45 and 190 mg/ℓ were reported for tidewater silversides, bluegills (Dawson et al., 1977) and goldfish (Bridie et al., 1979a), respectively.

Data related to the pharmacokinetics of 2-methoxyethanol acetate are very limited. From toxicity studies, absorption of 2-methoxyethanol acetate through the skin, lung and gastrointestinal tract as well as general distribution throughout the body can be inferred. 2-Methoxyethanol acetate is most likely hydrolyzed to 2-methoxyethanol (Stott and McKenna, 1985; Dahl and Hadley, 1983; Hoffman, 1984; Browning, 1965), although there were no *in vivo* data available to support this conclusion. No excretion data were available.

No information is available regarding either the carcinogenicity or teratogenicity of 2-methoxyethanol acetate in animals or humans. 2-Methoxyethanol acetate reportedly caused aneuploidy in yeast (Zimmerman et al., 1985), but there is considerable doubt as to the relevance of these data to actual genotoxicity.

The only study that demonstrates the in vivo toxicity of 2-methoxyethanol acetate was conducted by Nagano et al. (1979), who treated male MCL-ICR mice at oral doses of 62.5, 125, 250, 500, 1000 or 2000 mg/kg/day, 5 days/week for 5 weeks. Significant decreases in testicular weight and substantial atrophy were observed in animals receiving $\geq$500 mg/kg. In addition, leukopenia was evident in mice in the 1000 and 2000 mg/kg groups. No effects were observed at $\leq$250 mg/kg/day. These responses were similar qualitatively and quantitatively (on a molar basis) to those induced by 2-methoxyethanol in the same study.

Oral LD_{50} values for 2-methoxyethanol acetate range from 1.25 g/kg in guinea pigs to 3.93 g/kg in rats (Smyth et al., 1941). Similar results were obtained following subcutaneous injection (Smyth et al., 1941; Flury and Wirth, 1933). Kidney lesions were common following these exposures. Three repeated 8-hour inhalation exposures of 1000 ppm (4831 mg/m^3) were generally lethal to cats, rabbits, guinea pigs and mice (Gross, 1938). Humans were unable to tolerate exposure to 1000 ppm (4831 mg/m^3) for 1 hour, while a level of 120 ppm (580 mg/m^3) for 3 minutes "provided good warning properties" (Union Carbide, 1958).

An inhalation study by Miller et al. (1982) was used by U.S. EPA (1986c) to derive an RfD for 2-methoxyethanol. This RfD was based on a NOEL for both developmental and testicular effects. Since 2-methoxyethanol acetate is metabolized to 2-methoxyethanol and the Nagano et al. (1979) study

reported effects quantitatively and qualitatively similar (on a molar basis) for both compounds, an RfD of 0.002 mg/kg/day or 0.11 mg/day for a 70 kg man is proposed based on analogy to 2-methoxyethanol. A CS of 23 and an RQ of 100 were derived from a chronic human MED of 28 mg/day based on neurochemical alterations in offspring of male rats exposed to 25 ppm (78 mg/m^3) of 2-methoxyethanol, 7 hours/day for 6 weeks in the study by Nelson et al. (1984). To calculate the MED, the exposure level of 78 mg/m^3 of 2-methoxyethanol was adjusted to 121 mg/m^3 for 2-methoxyethanol acetate. In terms of carcinogenic potential, 2-methoxyethanol acetate is classified as a U.S. EPA Group D chemical, meaning there is inadequate evidence or in this case no existing data regarding the human carcinogenicity of this compound.

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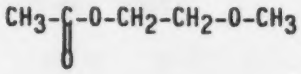
LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
BOD	Biochemical oxygen demand
CNS	Central nervous system
COD	Chemical oxygen demand
CS	Composite score
DNA	Deoxyribonucleic acid
K_{oc}	Soil sorption coefficient
K_{ow}	Octanol water partition coefficient
LC_{50}	Median lethal concentration
LD_{50}	Median lethal dose
LOAEL	Lowest-observed-adverse-effect level
MED	Minimum effective dose
MLD	Minimum lethal dose
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
PEL	Permissible exposure level
ppm	Parts per million
RfD	Reference dose
RQ	Reportable quantity
RV_d	Dose-rating value
RV_e	Effect-rating value
ThOD	Theoretical oxygen demand
TLV	Threshold limit value

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

2-Methoxyethanol acetate is also known as 2-methoxyethyl acetate, ethylene glycol monomethyl ether acetate, acetyl methyl cellosolve and methyl cellosolve acetate. The structure, molecular weight, empirical formula and CAS Registry number for 2-methoxyethanol acetate are as follows:



Molecular weight: 118.13

Empirical formula: $C_5H_{10}O_3$

CAS Registry number: 110-49-6

1.2. PHYSICAL AND CHEMICAL PROPERTIES

2-Methoxyethanol acetate is a colorless liquid at room temperature, with a sweet, pleasant odor (Verschueren, 1983; Hawley, 1981). It is miscible with common organic solvents and is incompatible with nitrates, strong oxidizers, strong acids and strong alkalies (Hawley, 1981; U.S. EPA, 1982). 2-Methoxyethanol acetate is a moderate fire hazard when exposed to heat or flame and, in case of fire, will form toxic gases and vapors such as carbon monoxide (Hawley, 1981; U.S. EPA, 1982). Selected physical properties of 2-methoxyethanol acetate are listed below.

Melting point:	-65.1°C	Union Carbide, 1979
Boiling point:	145°C (760 mm Hg)	Union Carbide, 1979
Vapor pressure:	2 mm Hg at 20°C	Union Carbide, 1979
Water solubility:	complete	Union Carbide, 1979
Log K_{ow}:	0.12	U.S. EPA, 1986a

Vapor density: (air=1)	4.07	U.S. EPA, 1982
Specific gravity:	1.0067 (20/20°C)	Union Carbide, 1979
Refractive index, n_d^{20}:	1.4019	Brown et al., 1980
Flashpoint:	121°F (49.4°C) (closed cup)	Union Carbide, 1979
	132°F (55.6°C (open cup)	Brown et al., 1980
TLV, air:	25 ppm (skin)	Sax, 1984
Conversion factors in air:	1 mg/m³ = 0.207 ppm 1 ppm = 4.83 mg/m³	

1.3. PRODUCTION DATA

2-Methoxyethanol acetate is produced from ethylene glycol monoethyl ether, by first reacting ethylene oxide and anhydrous methanol under a variety of reaction conditions and with or without catalysts such as caustic soda or boron trifluoride. Monoethers of diethylene, triethylene and polyethylene glycols are by-products of the reaction. The ethylene glycol monomethyl ether is then esterified with acetic acid to produce 2-methoxyethanol acetate (U.S. EPA, 1982).

Since 1984, Union Carbide Corp. (Chemicals and Plastic Div.), South Charleston, WV, has been the only U.S. manufacturer of 2-methoxyethanol acetate (USITC, 1985). The U.S. manufacturers and importers of this chemical in 1977 are listed in Table 1-1. The current production volume of 2-methoxyethanol acetate could not be located in the available literature.

1.4. USE DATA

2-Methoxyethanol acetate is used primarily as a solvent for oils, greases, inks, gums, resins, plastics, adhesives, waxes, nitrocellulose, cellulose acetate and other cellulose esters and ethers (U.S. EPA, 1982).

TABLE 1-1

U.S. Manufacturers and Importers of 2-Methoxyethanol Acetate for 1977[a]

Company/Location	Manufacturer or Importer	Volume Produced or Imported
Union Carbide Corp. South Charleston, WV	manufacturer	confidential
CPS Chemical Co. Oldbridge, NJ	manufacturer	none[b]
Ugine Kuhlmann of America, Inc. Paramus, NJ	importer	confidential

[a]Source: U.S. EPA, 1978

[b]This company manufactured 2-methoxyethanol before 1977

It is also used in the textile printing industry and in the manufacture of lacquers, enamels, adhesives and photographic film (U.S. EPA, 1982).

2-Methoxyethanol acetate is used in a resin/water mixture to prevent discoloration of dyes of thermoplastic moldings; for the control of oil spills; as a final rinse of resist patterns; as a rinse after the electrophoretic coating of metals; in the formation of a protective layer on X-ray intensifying screens; for treating defective lacquer coatings on cars; to impart stability to organophosphate insecticides; and as a stabilizer to absorb nitrogen oxides and sulfur dioxide in flue gas (U.S. EPA, 1982).

1.5. SUMMARY

2-Methoxyethanol acetate, also known as ethylene glycol monomethyl ether acetate, is a colorless liquid at room temperature, with a sweet, pleasant odor. It is miscible with water and many common organic solvents (Verschueren, 1983; Hawley, 1981). Ethylene glycol monomethyl ether, formed by reacting ethylene oxide and anhydrous methanol, is esterified with acetic acid to produce 2-methoxyethanol acetate (U.S. EPA, 1982). Since 1984, Union Carbide Corp., South Charleston, WV, has been the only U.S. manufacturer of 2-methoxyethanol acetate. The current U.S. production volume for this chemical is unavailable.

The primary use of 2-methoxyethanol acetate is as a solvent for oils, greases, inks, gums, resins, plastics, adhesives, waxes, nitrocellulose, cellulose acetate and other cellulose esters and ethers. 2-Methoxyethanol acetate is also used in the manufacture of lacquers, enamels, adhesives, photographic film and in the textile printing industry (U.S. EPA, 1982).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

Pertinent data regarding the environmental fate and transport of 2-methoxyethanol acetate in water, air and soil could not be located in the available literature as cited in the Appendix. When possible, physical properties and the limited laboratory studies of related compounds were used to derive information on the environmental fate and transport processes of 2-methoxyethanol acetate.

2.1. WATER

2.1.1. Hydrolysis. Carboxylic acid esters are potentially susceptible to hydrolysis (Lyman et al., 1982). Based on the molecular structure of 2-methoxyethanol acetate, hydrolysis may be a potential removal process in the ambient environment; however, the hydrolysis half-lives of ethyl acetate in water at 25°C and at pHs of 7 and 9 were estimated to be 2 years and 7 days, respectively (Lyman et al., 1982). Therefore, the hydrolysis of 2-methoxyethanol in ambient water may be important.

2.1.2. Microbial Degradation. Bridie et al. (1979a) conducted a 5-day BOD test on 2-methoxyethanol acetate in accordance with the American Public Health Association standard dilution methods. The BOD value determined was 0.49 g O_2/g compound, which is 30% of the theoretical value. This BOD value suggests that 2-methoxyethanol acetate is slightly to moderately biodegradable. Analysis of a 10-day BOD value indicates that during incubation of 200-1000 mg/ℓ 2-methoxyethanol acetate in acclimated activated sludge, removal was 15%, suggesting that only slight biodegradation occurred (Ludzack and Ettinger, 1960). In a "dispersed seed aeration" study, Mills and Stack (1954) measured a 10-day BOD of 1.1 g O_2/g compound (68% ThOD),

which suggests that biodegradation was significant. The importance of biodegradation in natural waters is uncertain because of the conflicting results from the BOD studies and the lack of natural water studies.

2.1.3. Transport.

2.1.3.1. BIOACCUMULATION -- The complete water solubility and estimated log K_{ow} value of 0.12 of 2-methoxyethanol acetate suggest that significant bioaccumulation in aquatic organisms would not occur. The BCF has been estimated from the K_{ow} by using the equation (Lyman et al., 1982): log BCF = 0.76 log K_{ow} - 0.23. The calculated BCF value of 0.73 suggests insignificant bioaccumulation of 2-methoxyethanol acetate in aquatic organisms.

2.1.3.2. ADSORPTION -- The complete water solubility and log K_{ow} value of 0.12 for 2-methoxyethanol acetate suggest that adsorption to particulate organic matter and sediment in water will not be significant.

2.1.3.3. VOLATILIZATION -- Although the compound has a vapor pressure of 2 mm Hg at ambient temperatures, it is difficult to predict its volatility from water because of its complete miscibility in water.

2.2. AIR

Because of its vapor pressure (2 mm Hg at 20°C) under any atmospheric conditions 2-methoxyethanol acetate should exist primarily in the vapor phase. The compound has demonstrated moderate reactivity in smog chamber studies in which it was irradiated by black lights (Yanagihara et al., 1977). The estimated rate constant for 2-methoxyethanol acetate reacting with photo- chemically generated HO radical is 1.073×10^{-11} cm^3 $molecule^{-1}$ sec^{-1} at 25°C (U.S. EPA, 1986b). Assuming an ambient HO radical concentration of 8.0×10^5 molecules cm^{-3} (U.S. EPA, 1986b), the HO radical reaction half-life has been estimated to be 22.42 hours. 2-Methoxyethanol acetate is predicted to not react with ozone (U.S. EPA,

1986b). Considering the complete water solubility of 2-methoxyethanol acetate, removal from the atmosphere by wet deposition may be significant.

2.3. SOIL

2.3.1. Hydrolysis. Hydrolysis of 2-methoxyethanol acetate may be a potential removal process particularly in moist basic soils (see Section 2.1.1.).

2.3.2. Leaching. The complete water solubility and K_{ow} value of 2-methoxyethanol acetate suggest that it may leach readily in the soil. Using the molecular topology and quantitative structure-activity relationship analysis method of Sabljic (1984), a K_{oc} of 94 can be predicted for 2-methoxyethanol acetate, indicating high soil mobility (Swann et al., 1983). 2-Methoxyethanol acetate may be removed by hydrolysis in moist soils, where it is expected to be highly mobile.

2.3.3. Volatilization. n-Butyl acetate undergoes 100% weight loss in 8 minutes from glass surfaces during a standard evaporation test conducted at 77°F and 15% relative humidity (Dow Chemical Co., 1981). The relative evaporation rate (n-butyl acetate=1) for 2-methoxyethanol acetate is 0.3 (Smith, 1984), which suggests that 2-methoxyethanol would evaporate quite rapidly from dry soil, assuming no significant adsorption to soil.

2.4. SUMMARY

In water, the two important processes that may remove 2-methoxyethanol are hydrolysis and biodegradation (Lyman et al., 1982). Bioaccumulation in aquatic organisms and adsorption to suspended solids and sediments should not be significant. The compound is expected to persist in water. In the atmosphere, 2-methoxyethanol acetate is expected to exist primarily in the vapor phase and is apparently susceptible to oxidation by HO radical

($t_{1/2}$=22.42 hours) (Yanagihara et al., 1977; U.S. EPA, 1986b). Removal from the atmosphere by wet deposition may also be significant. In soil, 2-methoxyethanol acetate should be highly mobile in moist soils and may volatilize significantly from dry soil surfaces. This compound may be degraded in moist soils by hydrolysis and biodegradation.

3. EXPOSURE

Limited monitoring and exposure data regarding 2-methoxyethanol acetate were located in the available literature. 2-Methoxyethanol acetate has been qualitatively identified in drinking water (Kool et al., 1982) and in effluents discharged into the Illinois River (Somani et al., 1980). Consumer exposure to this compound would likely occur during the use of cleaning solutions, paint, ink and nail polish that contain 2-methoxyethanol acetate (U.S. EPA, 1982).

Potential routes of 2-methoxyethanol acetate exposure to workers include inhalation of the vapor, ingestion and eye and skin contact (U.S. EPA, 1982). A 1972-1974 National Occupational Hazard Survey estimated that 436,989 workers are occupationally exposed to this compound during manufacturing, processing, use and handling of 2-methoxyethanol acetate (RTECS, 1984). A more recent survey, the National Occupational Exposure Survey, estimates that 2024 workers are exposed to 2-methoxyethanol acetate; however, this figure does not reflect exposure to tradename products containing 2-methoxyethanol acetate (NIOSH, 1985).

4. PHARMACOKINETICS

4.1. ABSORPTION

Pertinent data regarding the absorption of 2-methoxyethanol acetate could not be located in the available literature as cited in the Appendix. Systemic toxicity resulting from acute exposures (Chapter 5), however, suggests that absorption does occur to some extent following oral, inhalation or dermal exposure to 2-methoxyethanol acetate. Rowe and Wolf (1982) stated that 2-methoxyethanol acetate can be absorbed through the skin with prolonged contact.

4.2. DISTRIBUTION

Although little is known of the specific distribution of 2-methoxyethanol acetate, apparently it is generally distributed throughout the body since effects in the blood, testes, brain and kidney have been reported following exposure.

4.3. METABOLISM

The limited data available concerning the metabolism of 2-methoxyethanol acetate pertain only to in vitro experimentation. Hoffman (1984) reported that 2-methoxyethanol acetate is readily hydrolyzed by rat plasma esterases. A half-life of ~10 minutes was determined for the acetate in plasma by gas-liquid chromatography. Stott and McKenna (1985) demonstrated that 2-methoxyethanol acetate was a relatively good substrate for carboxyesterases present in mouse nasal mucosa, liver, kidney, lung and blood. In addition, significant 2-methoxyethanol production resulted from incubation of 2-methoxyethanol acetate with nasal mucosal carboxyesterase from rats, rabbits and dogs. Incubation of 2-methoxyethanol acetate with nasal and liver microsomes from rats did not result in appreciable formaldehyde formation (Dahl and Hadley, 1983). Browning (1965) suggested that, like other

acid esters of the glycol ethers, 2-methoxyethanol acetate is saponified in the body giving rise to systemic effects similar to those caused by 2-methoxyethanol.

4.4. EXCRETION

Pertinent data regarding the excretion of 2-methoxyethanol acetate in animals could not be located in the available literature as cited in the Appendix.

4.5. SUMMARY

Data related to the pharmacokinetics of 2-methoxyethanol acetate are very limited. From toxicity studies, absorption of 2-methoxyethanol acetate through the skin, lung and gastrointestinal tract as well as general distribution throughout the body can be inferred. 2-Methoxyethanol acetate is most likely hydrolyzed to 2-methoxyethanol (Stott and McKenna, 1985; Dahl and Hadley, 1983; Hoffman, 1984; Browning, 1965), although there were no in vivo data available to support this conclusion. No excretion data were available.

5. EFFECTS

5.1. CARCINOGENICITY

Pertinent data regarding the carcinogenicity of 2-methoxyethanol acetate could not be located in the available literature as cited in the Appendix.

5.2. MUTAGENICITY

2-Methoxyethanol acetate strongly induced aneuploidy but not mitotic recombination or point mutation in the yeast Saccharomyces cerevisiae strain D61.M, but only at relatively high concentrations that ranged from 2.91-5.66% (Zimmerman et al., 1985). These authors suggested that this may not reflect 2-methoxyethanol acetate-induced changes in DNA or DNA-metabolizing systems, but rather may be the consequence of effects on the spindle apparatus. Further experiments were conducted on porcine brain tubulin in vitro, and it was demonstrated that 2-methoxyethanol acetate accelerated tubulin assembly at concentrations >100-fold lower than those needed to induce aneuploidy (Groschel-Stewart et al., 1985). The correlation between these two events is speculative, however, because of the species difference between porcine brain and yeast spindle tubulin and the large discrepancy in the concentrations needed to induce these changes. Additional data pertinent to 2-methoxyethanol acetate mutagenicity were not located.

5.3. TERATOGENICITY

Information concerning the potential teratogenic effects of 2-methoxyethanol acetate could not be located in the available literature as cited in the Appendix. In vitro studies have shown, however, that 2-methoxyethanol acetate is hydrolyzed to 2-methoxyethanol (see Section 4.3.), which is an established teratogen (U.S. EPA, 1986c).

5.4. OTHER REPRODUCTIVE EFFECTS

Nagano et al. (1979) investigated the testicular toxicity induced by 2-methoxyethanol in 6-week-old male JCL-ICR mice. The compound was diluted in water and administered orally by stomach tube to groups of five mice, 5 days/week for 5 weeks, at daily doses of 62.5, 125, 250, 500, 1000 or 2000 mg/kg. A control group of 20 mice was given water by the same method. A dose-related decrease in absolute and relative testes weight was observed; the decrease was statistically significant at doses $\geq$500 mg/kg. A significant decrease in the combined weights of the vesicular and coagulating glands was seen only in the high-dose group. Histopathological examination of the testes revealed dose-related atrophy of the seminiferous epithelium at $\geq$500 mg/kg. In the 500 mg/kg group, there was an obvious reduction in the number of spermatocytes. In the 1000 mg/kg group, spermatids and spermatozoa were not present, and the diameter of the seminiferous tubules was significantly reduced. Spermatocytes existed only in small numbers in some of the tubules. In the 2000 mg/kg group, no germ cells were observed, although Sertoli cells were present. This response was essentially equivalent on a molar basis to that observed with 2-methoxyethanol.

5.5. CHRONIC AND SUBCHRONIC EFFECTS

In the Nagano et al. (1979) study (see Section 5.4.), hematological data were also obtained. A significant decrease in the white blood cell count occurred in the 1000 and 2000 mg/kg dose groups, while a reduction in hemoglobin was seen only in the high dose mice. Changes in the red blood cell count and packed cell volume were less pronounced. No other pertinent data regarding the chronic or subchronic effects of 2-methoxyethanol acetate could be located in the available literature as cited in the Appendix.

5.6. OTHER RELEVANT INFORMATION

The acute toxicity of 2-methoxyethanol acetate in animals is summarized in Table 5-1. LD_{50} values of 3.93 g/kg for rats and 1.25 g/kg for guinea pigs were determined by feeding 50% aqueous solutions by stomach tube (Smyth et al., 1941). Gross pathology observations revealed effects on the kidney, liver and digestive tract. Rabbits died after receiving 3 daily oral doses of either 0.5 or 1.0 g/kg, and all exhibited signs of kidney injury with albumin and granular casts in the urine (Gross, 1938).

Gross (1938) conducted extensive studies on the acute inhalation toxicity of 2-methoxyethanol acetate in a number of species. Kidney injury was observed in cats, guinea pigs, rabbits and mice following repeated 8-hour exposures to 500 or 1000 ppm (2416 or 4831 mg/m³). At 500 ppm, cats showed slight narcosis and died, while at 1000 ppm, deaths occurred in all species. Cats were able to tolerate repeated 4- to 6-hour exposures to 200 ppm (966 mg/m³), although decreases in blood pigments and in the red blood cell count were observed. Cats were also able to survive a 7-hour exposure to 1500 ppm (7247 mg/m³), but did have an increase in blood clotting time and displayed changes in the brain. Cats died after being exposed to 2500 ppm (12,078 mg/m³) for 9 hours. Mice and rabbits survived a 3-hour exposure to 4554 ppm (22,000 mg/m³), an essentially saturated atmosphere. A similar 1-hour exposure resulted only in mucous membrane irritation in mice, rats, guinea pigs and rabbits. Dogs exposed to 2-methoxyethanol acetate vapor at a concentration of 400 ppm (1933 mg/m³), 8 hours/day for 120 days had minor disturbances in liver function (Union Carbide, 1958).

Five drops of undiluted 2-methoxyethanol acetate produced mild irritation in the eyes of a rabbit, while application to rabbit skin was not significantly irritating (Union Carbide, 1958).

TABLE 5-1

Acute Toxicity of 2-Methoxyethanol Acetate

Route	Species	Dose/Concentration	Response	Reference
Oral	rat	3.93 g/kg	LD_{50}	Smyth et al., 1941
	rabbit	0.5-1.0 g/kg, 3 daily doses	death	Gross, 1938
	guinea pig	1.25 g/kg	LD_{50}	Smyth et al., 1941
Inhalation	rat	7000 ppm (33,810 mg/m³) for 4 hours	death in 2/6 animals	Smyth and Carpenter, 1948
	rabbit, guinea pig	1000 ppm (4830 mg/m³) repeated 8-hour exposures	death	Gross, 1938
	cat	500 or 1000 ppm (2415 or 4830 mg/m³) repeated 8-hour exposures	death	Gross, 1938
	cat	2500 ppm (12,075 mg/m³) for 9 hours	death	Gross, 1938
Subcutaneous	guinea pig	5 g/kg	MLD	Flury and Wirth, 1933
	guinea pig	1.25 g/kg	LD_{50}	Smyth et al., 1941
	cat	3-4 g/kg	MLD	Flury and Wirth, 1933

Jordan and Dahl (1971) reported the case of a 58-year-old woman who developed acute dermatitis on the nose from contact with her eyeglasses. Patch testing demonstrated the causative agents to be 2-methoxyethanol acetate or ethyl acetate. This is the only recorded case of adverse effects in humans following exposure to 2-methoxyethanol acetate and the results are inconclusive. Exposure to 1000 ppm (4831 mg/m³) 2-methoxyethanol acetate for 1 minute was intolerable for volunteers, while a level of 120 ppm (580 mg/m³) for 3 minutes "provided good warning properties" (Union Carbide, 1958).

5.7. SUMMARY

No information is available regarding either the carcinogenicity or teratogenicity of 2-methoxyethanol acetate in animals or humans. 2-Methoxyethanol acetate reportedly caused aneuploidy in yeast (Zimmerman et al., 1985), but there is considerable doubt as to the relevance of these data to actual genotoxicity.

The only study that demonstrates the in vivo toxicity of 2-methoxyethanol acetate was conducted by Nagano et al. (1979), who treated male MCL-ICR mice at oral doses of 62.5, 125, 250, 500, 1000 or 2000 mg/kg/day, 5 days/week for 5 weeks. Significant decreases in testicular weight and substantial atrophy were observed in animals receiving $\geq$500 mg/kg. In addition, leukopenia was evident in mice in the 1000 and 2000 mg/kg groups. No effects were observed at $\leq$250 mg/kg/day. These responses were similar qualitatively and quantitatively (on a molar basis) to those induced by 2-methoxyethanol in the same study.

Oral LD_{50} values for 2-methoxyethanol acetate range from 1.25 g/kg in guinea pigs to 3.93 g/kg in rats (Smyth et al., 1941). Similar results were obtained following subcutaneous injection (Smyth et al., 1941; Flury and Wirth, 1933). Kidney lesions were common following these exposures. Three repeated 8-hour inhalation exposures of 1000 ppm (4831 mg/m³) were generally lethal to cats, rabbits, guinea pigs and mice (Gross, 1938). Humans were unable to tolerate exposure to 1000 ppm (4831 mg/m³) for 1 hour, while a level of 120 ppm (580 mg/m³) for 3 minutes "provided good warning properties" (Union Carbide, 1958).

6. AQUATIC TOXICITY

6.1. ACUTE

Little information is available regarding the effects of 2-methoxyethanol acetate on aquatic organisms. Dawson et al. (1977) reported that the 96-hour LC_{50} value for bluegills, Lepomis macrochirus, was 45 mg/ℓ. No mortalities occurred at 10 mg/ℓ, while 10, 60 and 100% mortality occurred at 25, 50 and 100 mg/ℓ, respectively. Dawson et al. (1977) also determined a 96-hour LC_{50} value of 40 mg/ℓ for tidewater silversides, Menidia beryllina, with 100% mortality at 75 mg/ℓ, 70% at 50 mg/ℓ and 0% at 25 mg/ℓ. Bridie et al. (1979a) reported a 24-hour LC_{50} of 190 mg/ℓ for the goldfish, Carassius auratus.

6.2. CHRONIC

Pertinent data regarding the chronic toxicity of 2-methoxyethanol acetate could not be located in the available literature as cited in the Appendix.

6.3. PLANTS

Pertinent data regarding the effects of 2-methoxyethanol acetate on aquatic plants could not be located in the available literature as cited in the Appendix.

6.4. RESIDUES

Pertinent data regarding 2-methoxyethanol acetate residues in aquatic biota could not be located in the available literature as cited in the Appendix.

6.5. SUMMARY

Little information is available concerning the effects of 2-methoxyethanol acetate on aquatic organisms. LC_{50} values of 40, 45 and 190 mg/ℓ were reported for tidewater silversides, bluegills (Dawson et al., 1977) and goldfish (Bridie et al., 1979a), respectively.

7. GUIDELINES AND STANDARDS

7.1. HUMAN

ACGIH (1985-1986) adopted a TLV for 2-methoxyethanol acetate of 5 ppm (24 mg/m^3), based upon the reported testicular effects and the apparent hydrolysis of the ester to 2-methoxyethanol (ACGIH, 1986). OSHA (1985) has established a PEL of 25 ppm (120 mg/m^3), the same as recommended for the parent glycol ether. Both of these recommendations are accompanied by the "skin" notation, indicating that dermal absorption is a potentially hazardous route of exposure.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic biota from the effects of 2-methoxyethanol acetate could not be located in the available literature as cited in the Appendix.

8. RISK ASSESSMENT

Pertinent data regarding either the carcinogenicity or teratogenicity of 2-methoxyethanol acetate in animals or humans could not be located in the available literature. Therefore, because of the lack of carcinogenic data, this compound is classified as a U.S. EPA Group D chemical (i.e., its carcinogenic potential is not ascertainable). 2-Methoxyethanol acetate reportedly caused aneuploidy in yeast (Zimmerman et al., 1985), but there is considerable doubt as to the relevance of these data to actual genotoxicity.

The only study that demonstrates the in vivo toxicity of 2-methoxyethanol acetate was conducted by Nagano et al. (1979), who treated male JCL-ICR mice at oral doses of 62.5, 125, 250, 500, 1000 or 2000 mg/kg/day, 5 days/week for 5 weeks. Significant decreases in testicular weight and substantial atrophy were observed in animals receiving $\geq$500 mg/kg. In addition, leukopenia was evident in mice in the 1000 and 2000 mg/kg groups. No significant adverse effects were observed at doses of $\leq$250 mg/kg. These responses were similar qualitatively and quantitatively (on a molar basis) to those induced by 2-methoxyethanol in the same study.

Based on the available information regarding the adverse effects of 2-methoxyethanol (U.S. EPA, 1986c) and the evidence that 2-methoxyethanol acetate is hydrolyzed to the parent glycol ether, it is not prudent to base an RfD for 2-methoxyethanol acetate on the data provided by Nagano et al. (1979). A NOEL of 250 mg/kg/day, 5 days/week (179 mg/kg/day), as established by this study, is not adequately protective if 2-methoxyethanol acetate produces teratogenic, fetotoxic and reproductive effects at doses equimolar to those of 2-methoxyethanol producing such effects. Thus, an RfD for 2-methoxyethanol acetate can be derived based on the RfD for 2-methoxy-

ethanol. This procedure is similar to that proposed by ACGIH (1986) for establishing a TLV for 2-methoxyethanol acetate. No chronic oral or inhalation studies on 2-methoxyethanol are available; also no studies regarding the subchronic oral toxicity are available. Oral studies regarding the teratogenic and reproductive effects of 2-methoxyethanol are available; however, a NOEL or NOAEL could not be established from these studies (U.S. EPA, 1986c). Subchronic inhalation studies by Miller et al. (1982, 1983), however, established a NOEL of 10 ppm, 6 hours/day, 5 days/week in rabbits (converted to 1.46 mg/kg/day) and a LOAEL of 30 ppm, 6 hours/day, 5 days/week in rabbits (converted to 4.57 mg/kg/day) for testicular lesions and developmental effects. Dividing the NOEL by an uncertainty factor of 1000 resulted in an RfD for 2-methoxyethanol of 0.001 mg/kg/day or 0.01 mg/day for a 70 kg man.

An RfD of 0.002 mg/kg/day or 0.11 mg/day for a 70 kg man can be derived for 2-methoxyethanol acetate by analogy to 2-methoxyethanol by multiplying the RfD for 2-methoxyethanol by the molecular weight ratio of 2-methoxyethanol to 2-methoxyethanol acetate.

9. REPORTABLE QUANTITIES

9.1. REPORTABLE QUANTITY (RQ) RANKING BASED ON CHRONIC TOXICITY

Only one subchronic toxicity study of 2-methoxyethanol acetate was available (Nagano et al., 1979). This study was discussed in Section 5.4. and is summarized in Table 9-1. The 500 mg/kg/day, 5 days/week (357 mg/kg/day) exposure was the lowest dose in the study to cause reduced spermatogenesis. Multiplying the dose of 357 mg/kg/day by the cube root of the ratio of the mouse body weight (0.03 kg) to the reference human body weight to convert to an equivalent human dose and by 70 kg to express the dose in mg/day and dividing by 10 to approximate chronic exposure results in an MED of 188 mg/day (Table 9-2). The MED corresponds to an RV_d of 2.1. The effect of reduced spermatogenesis warrants an RV_e of 8, which when multiplied by the RV_d yields a CS of 17, corresponding to an RQ of 1000. Mice at $\geq$1000 mg/kg/day also had hematological effects, but since these effects warranting lower RV_es were observed at higher doses, calculation of CSs is not necessary.

Since 2-methoxyethanol has been studied for teratogenic and reproductive effects more extensively than 2-methoxyethanol acetate, and since 2-methoxyethanol acetate is believed to produce similar effects as 2-methoxyethanol on an equimolar basis, it is more appropriate to derive the RQ for the acetate by analogy to the more studied compound. U.S. EPA (1986c) derived an RQ of 100 for 2-methoxyethanol based on a 6-week inhalation study by Nelson et al. (1984) using Sprague-Dawley rats. In this study, the 21-day offspring of male rats exposed to 25 ppm (78 mg/m^3) of 2-methoxyethanol, 7 hours/day, 7 days/week for 6 weeks had neurochemical deviations in the brain. An RV_e of 7 was assigned. The exposure level of 25 ppm (78 mg/m^3) corresponds to 121 mg/m^3 of 2-methoxyethanol acetate. Expanding

TABLE 9-1

Oral Toxicity Summary for 2-Methoxyethanol Acetate Using Male JCL-ICR Mice[a,b]

No. at Start	Average Weight (kg)	Vehicle/ Physical State	Exposure	Transformed Animal Dose (mg/kg/day)	Response
5/group	0.03	water	62.5, 125, 250 500, 1000 or 2000 mg/kg/day, 5 days/week for 5 weeks	45, 89, 179, 357, 714 or 1429	Significantly reduced absolute and relative testes weight at ≥500 mg/kg; dose-related atrophy of seminiferous epithelium at 500 mg/kg; at 500 mg/kg reduction in number of spermatocytes; at 1000 mg/kg no spermatids or spermatozoa present; at 2000 mg/kg, Sertoli cells only were present; leukopenia at ≥1000 mg/kg/day; reduced hemoglobin at 2000 mg/kg/day

[a]Source: Nagano et al., 1979

[b]Purity of compound was not reported

TABLE 9-2

Composite Scores for 2-Methoxyethanol Acetate

Route	Species	Animal Dose (mg/kg/day)	Chronic Human MED (mg/day)	RV_d	Effect	RV_e	CS	RQ	Reference
Oral	mouse/ JCL-ICR	357	188[a]	2.1	depressed spermatogenesis	8	17	1000	Nagano et al., 1979
Inhalation	rat/Sprague-Dawley	23[b]	28[a]	3.3	neurochemical deviations in offspring	7	23	100	Nelson et al., 1984

[a]An uncertainty factor of 10 was incorporated to extrapolate to a chronic human MED.

[b]The administered compound was 2-methoxyethanol, but the dose is expressed as 2-methoxyethanol acetate.

the exposure of 121 mg/m³ over a 24-hour day, multiplying by the rat breathing volume of 0.225 m³/day, which was calculated for the rat body weight in the study of 0.355 kg according to the method in U.S. EPA (1980), and dividing by the rat body weight results in a transformed dose of 23 mg/kg/day. Multiplying the transformed dose by the cube root of the ratio of the rat body weight to the human body weight and 70 kg and dividing by an uncertainty factor of 10 to approximate chronic exposure yields the MED of 28 mg/day. The MED corresponds to an RV_d of 3.3, which when multiplied by the RV_e of 7, yields a CS of 23, corresponding to an RQ of 100. The Nelson et al. (1984) study is recommended as the basis for the RQ for 2-methoxyethanol acetate (Table 9-3).

9.2. WEIGHT OF EVIDENCE AND POTENCY FACTOR ($F=1/ED_{10}$) FOR CARCINOGENICITY

There are no data available concerning the carcinogenicity of 2-methoxyethanol acetate. According to the U.S. EPA (1986d), this compound is most appropriately classified as a Group D chemical meaning that there is inadequate evidence to classify this compound regarding its potential human carcinogenicity.

TABLE 9-3

2-Methoxyethanol Acetate
Minimum Effective Dose (MED) and Reportable Quantity (RQ)[a]

Route:	inhalation
Dose[b]:	28 mg/day
Effect:	neurochemical deviations in offspring
Reference:	Nelson et al., 1984
RV_d:	3.3
RV_e:	7
Composite Score:	23
RQ:	100

[a]The derivation is based on data for 2-methoxyethanol. The dose is expressed as 2-methoxyethanol acetate.

[b]Equivalent human dose

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APPENDIX

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of the following:

GLOBAL
TSCATS
CASR online (U.S. EPA Chemical Activities Status Report)
CAS online STN International
TOXLINE
TOXBACK 76
TOXBACK 65
RTECS
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE
TSCAPP
NTIS
Federal Register

These searches were conducted in April, 1986. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1986. Documentation of the Threshold Limit Values and Biological Exposure Indices, 5th ed. Cincinnati, OH.

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Worthing, C.R. and S.B. Walker, Ed. 1983. The Pesticide Manual. British Crop Protection Council. 695 p.

In addition, approximately 30 compendia of aquatic toxicity data were reviewed, including the following:

Battelle's Columbus Laboratories. 1971. Water Quality Criteria Data Book. Volume 3. Effects of Chemicals on Aquatic Life. Selected Data from the Literature through 1968. Prepared for the U.S. EPA under Contract No. 68-01-0007. Washington, DC.

Johnson, W.W. and M.T. Finley. 1980. Handbook of Acute Toxicity of Chemicals to Fish and Aquatic Invertebrates. Summaries of Toxicity Tests Conducted at Columbia National Fisheries Research Laboratory. 1965-1978. U.S. Dept. Interior, Fish and Wildlife Serv. Res. Publ. 137, Washington, DC.

McKee, J.E. and H.W. Wolf. 1963. Water Quality Criteria, 2nd ed. Prepared for the Resources Agency of California, State Water Quality Control Board. Publ. No. 3-A.

Pimental, D. 1971. Ecological Effects of Pesticides on Non-Target Species. Prepared for the U.S. EPA, Washington, DC. PB-269605.

Schneider, B.A. 1979. Toxicology Handbook. Mammalian and Aquatic Data. Book 1: Toxicology Data. Office of Pesticide Programs, U.S. EPA, Washington, DC. EPA 540/9-79-003. NTIS PB 80-196876.